Published by Elsevier Science Inc.

ISSN 0735-1097/03/$30.00
doi:10.1016/S0735-1097(02)02967-4

Age and Hemodynamic Responses to Tilt Testing in Those With Syncope of Unknown Origin

Arvinder S. Kurbaan, MD,* Timothy J. Bowker, MD,† Nevin Wijesekera, MB,†
Ann-Christine Franzén, RGN,‡ David Heaven, MB,‡ Sujani Itty, MB,‡ Richard Sutton, DSCMED, FACC‡
London, United Kingdom

OBJECTIVES We sought to determine whether there are age-related differences in vasovagal syncope.

BACKGROUND In those with suspected vasovagal (neurocardiogenic) syncope, tilt testing demonstrates different hemodynamic responses. These responses may be age related, reflecting differing underlying pathophysiology.

METHODS Using a two-stage tilt protocol with glyceryl trinitrate (GTN) provocation, 505 consecutive syncopal patients were studied. Their baseline characteristics and hemodynamic responses during both early and tilt-induced collapse were analyzed. Hemodynamic responses were classified using the VAsovagal Syncope International Study (VASIS) criteria: mixed, cardioinhibition, severe cardioinhibition/asystole, pure vasodepression, chronotropic incompetence, and excessive heart rate rise. Multivariate regression analyses were performed to determine the associations of the baseline clinical characteristics (including age) and the tilt-induced hemodynamic responses.

RESULTS Thirty-three patients were unable to tolerate tilt testing. Age was independently associated with distinct responses during tilt. Chronotropic incompetence was predicted by increasing age (odds ratio [OR] 1.04, $p < 0.0002$). Younger age predicted an excessive heart rate rise (OR 0.97, $p < 0.0005$). Pure vasodepression was more common in the older group (>65 years; OR 29.5, $p < 0.0001$), whereas severe cardioinhibition was much less common in the older age group (OR 0.18, $p < 0.0001$).

CONCLUSIONS There appear to be distinct pathophysiologies underlying vasovagal syncope in different age groups. Young people appear to have excessive cardiac and autonomic responses to stress, whereas older patients appear to have a more generalized cardiovascular decline, with attenuated cardiac and autonomic responses to stress. (J Am Coll Cardiol 2003;41:1004–7)

In those with syncope of unknown origin but a suspected vasovagal (neurocardiogenic) pathophysiology, tilt testing with drug provocation has become an integral part of the assessment (1–3). Recently, attention has focused on the heart rate (HR) and blood pressure (BP) (hemodynamic) responses that patients display while attempting to maintain an upright posture during the tilt test and, ultimately, during collapse (3–5). These hemodynamic patterns have been classified by the VAsovagal Syncope International Study (VASIS) into distinct subgroups based on these HR and BP responses (4). The diverse nature of the responses seen suggests that there may be differences in the underlying pathophysiology (5). How these different hemodynamic responses relate to age remains less well studied. In this study, we assessed whether there are distinct associations between different tilt-induced hemodynamic patterns and age. This has implications not only for the understanding of vasovagal syncope but also for more effective targeting of therapy.

METHODS

Study population. Patients with one or more syncopal attacks were diagnosed as having unexplained syncope if no cause was found after a standard diagnostic evaluation. This consisted of a careful history and physical examination, full clinical neurologic assessment, routine laboratory tests, supine and orthostatic BP measurements, and a 12-lead electrocardiogram consistent with the European Society of Cardiology Task Force on Syncope (6). Patients who had no evidence of structural heart disease or whose disease was sufficiently mild not to require specific therapy (e.g., aortic stenosis treated by valve replacement) were included. Using this diagnostic approach, other interventions, such as electrophysiologic study, were not performed before the tilt test.

Head-up tilt testing. The tilt test was performed by means of an electrically controlled tilt table with a footboard for weight bearing. Blood pressure, HR, and rhythm were continuously monitored and recorded. Heart rate data were obtained as a series of R-R intervals with resolution of 1 ms. Blood pressure was measured by means of either a Finapress 2300 (Ohmeda, Louisville, Colorado) or Portapres (TNO-

From the *Department of Cardiology, London Chest Hospital, London; †Department of Cardiology, St Mary's Hospital, London; and ‡Department of Cardiology, Chelsea & Westminster Hospital, London, United Kingdom. Richard Sutton is a neurally mediated syncope consultant to Medtronic, Inc. (Minneapolis, Minnesota). This study was commercially funded by Medtronic, Inc. (Minneapolis, Minnesota).

Manuscript received February 8, 2002; revised manuscript received August 7, 2002, accepted November 27, 2002.

Abbreviations and Acronyms

BP = blood pressure
CI = confidence interval
GTN = glyceryl trinitrate
HR = heart rate
OR = odds ratio
VASIS = VAsovagal Syncope International Study

BMI Amsterdam, The Netherlands) photoplethysmographic device, which provide continuous non-invasive beat-to-beat determination of finger arterial pressure by the Penàz (7) volume-clamp method, which accurately reflects changes (8). No invasive instrumentation was used during stress.

The two-stage tilt protocol with glyceryl trinitrate (GTN) provocation. The head-up tilt test was performed after an initial observation with the patient in the supine position for 10 min. The test consisted of two consecutive stages. In stage 1, patients were tilted at 60° for up to 45 min without medication, in accordance with the Westminster drug-free protocol (1). If syncope (or limiting symptoms) did not develop, patients entered stage 2. They received 300 to 400 μg sublingual GTN and continued to be tilted for another 20 min. If syncope (or limiting symptoms) occurred during the test, the tilt table was rapidly adjusted to return the patient to the supine position, and the study was terminated.

Data collection and processing. Data were obtained for a supine rest period of 10 min throughout the period of tilt, and for 2 min after return to the supine position. Data from each patient were reviewed and edited manually to remove artifacts. Then, HR and BP were averaged for the rest period, for each minute of the tilt, and for the post-tilt period.

Data statistical analysis. BASELINE VARIABLES. Age was analyzed both as a continuous variable and as a discrete variable, with the population being divided into three groups: those ≤35 years old; 36 to 64 years; and ≥65 years. The other independent variables adjusted for were female gender, history of heart disease, postural hypotension, and use of GTN provocation.

CLASSIFICATION OF THE COLLAPSE PATTERN. There were six potential outcomes of tilt testing: a positive result (with four sub-classes), a negative result, or incomplete. A test was considered incomplete if the patient could not complete the tilt-test protocol. In those who completed the tilt test, a result was considered positive if the patient had syncope or limiting symptoms (i.e., collapse) during tilt testing. All the positive tests were classified according to the VASIS classification (4). The VASIS study classifies the collapse according to the pattern of BP and HR changes, the changes in early tilting, and carotid sinus syndrome, summarized as follows: type 1—mixed BP and HR fall without severe bradycardia; type 2A—cardioinhibition (BP falls before HR); type 2B—severe cardioinhibition (HR falls before or coincident with BP and/or asystole); type 3—BP falls without HR falling. In addition, there are atypical HR responses: chronotropic incompetence (minimal or no rise in HR [i.e., <10% increase from the supine pre-tilt level]) or an excessive HR rise before syncope (i.e., >130 beats/min). These criteria have recently been modified (5), but the modifications were not used in the present study.

LOGISTIC REGRESSION MODELING. The logistic regression modeling analysis was undertaken in two parts: 1) Predictors of atypical HR responses in early tilt testing. In part 1, the outcomes of interest were the two atypical HR responses in early tilt. The baseline clinical variables (e.g., age, gender, and so forth) were assessed as potential independent variables/predictors of these atypical HR responses. 2) Predictors of the final outcomes of tilt testing. In part 2, the outcomes of interest were six final outcomes. The baseline variables and the two atypical HR responses were assessed as potential independent variables/predictors of these final outcomes.

During logistic regression modeling, the criteria for acceptance were, first, the odds ratio (OR) with its 95% confidence interval (CI) and p value of each of the independent variables and, second, the p value of the Hosmer-Lemeshow goodness-of-fit chi-squared test of the model.

RESULTS

A total of 505 consecutive patients were studied. Of these, 33 (6.3%) were unable to tolerate tilt testing, usually for reasons of musculoskeletal discomfort, and their results were classified as incomplete; hence, 472 patients completed the protocol. Patients were grouped according to age. Table 1 shows the distribution of the baseline clinical characteristics, two atypical HR responses, and six final outcomes during tilt testing by age group.

Predictors of atypical HR responses in early tilt testing. Using logistic regression, chronotropic incompetence was predicted by increasing age (OR 1.04, 95% CI 1.02 to 1.07; $p < 0.0002$), whereas decreasing age predicted an excessive HR rise (OR 0.97, 95% CI 0.95 to 0.98; $p < 0.0005$).

Predictors of final outcomes of tilt testing. Older age was associated with an incomplete tilt test and pure vasodepression. Younger age was associated with severe cardioinhibition. The associations between the six final outcomes and age group are shown in Table 2. The quoted p value is that for the stepwise inclusion (or exclusion) of the age variable as a whole in (or from) the given logistic regression model. The modeling process does not provide separate p values for each individual level within the age variable, but it does provide individual ORs and 95% CIs for each level with respect to the lowest level (within the age variable).

Table 1. Distribution of Baseline Characteristics, Atypical Heart Rate Responses in Early Tilt Testing, and Final Outcomes Between the Age Groups

Characteristic or Tilt Response/Outcome	≤35 years (n = 165)	36–64 years (n = 169)	≥65 years (n = 171)	p Value*
Female (n = 259)	56.4	42.0	55.6	0.013
Heart disease (n = 69)	0	8.9	31.6	< 0.0005
Postural hypotension (n = 43)	1.8	3.6	19.9	< 0.0005
GTN provocation necessary (n = 280)	47.3	59.8	59.1	0.036
Chronotropic incompetence (n = 31)	0.0	5.9	12.3	< 0.0005
Excessive heart rate rise (n = 63)	24.9	7.1	5.9	< 0.0005
Unable to tolerate tilt testing (n = 33)	1.8	8.9	8.8	0.012
Negative result (n = 104)	15.1	26.0	20.5	0.049
Mixed response (VASIS-1) (n = 194)	43.6	37.9	33.9	0.185
Cardioinhibitory response (VASIS-2A) (n = 54)	5.5	9.5	9.9	0.265
Severe cardioinhibitory response/asystole (VASIS-2B) (n = 89)	33.3	14.8	5.3	< 0.0005
Pure vasodepression (VASIS-3) (n = 43)	0.6	3.0	21.6	< 0.0005

*Conchran-Mantel Haenszel. Data are presented as the percentage of patients.
GTN = glyceryl trinitrate; VASIS = VAsovagal Syncope International Study, types 1, 2A, 2B, and 3.

DISCUSSION

Analysis of the hemodynamic responses during early tilt testing and at the time of collapse show age-related differences. There appears to be a gradient in the age-related hemodynamic responses from the young to the old age group (Table 1), with the middle group's responses being closer to those of the older rather than younger group. The middle and old groups were more likely to not be able to complete the tilt test. This was the effect of the greater likelihood of musculoskeletal and other non-cardiac comorbidities. There was a relatively consistent finding of a mixed (VASIS-1) response being present in ~40% of patients in all ages. The mixed (VASIS-1) response may represent a genuine sub-type of vasovagal response or responses with a distinct pathophysiology or pathophysiologies. However, it is possible that the mixed response represents a false-positive finding. In their study of normal subjects undergoing tilt testing, Petersen et al. (9) found that of the 16 (13% of total) with positive results, 14 had mixed (VASIS-1) responses.

In older patients, chronotropic incompetence was more frequent. This phenomenon has been previously demonstrated in those undergoing exercise stress testing (10) and in candidates for pacing with sino-atrial disease (11,12). The aging heart and/or autonomic nervous system are unable to make the appropriate compensatory HR changes for the stress induced by tilt testing. This may mirror the real world, where changes in cardiac loading are not compensated for by appropriate changes in HR, which is fixed. It is uncertain whether the heart or autonomic nervous system is the primary problem. The data suggest that it may be both. The increasing frequency of chronotropic incompetence with increasing age was independent of that of heart disease.

There also appear to be distinct findings in the younger patients. Younger patients were more likely to have extreme changes in HR. This may be an "excessive HR rise" seen in early tilt testing or severe cardioinhibition/asystole seen at the time of collapse. Thus, unlike older patients, younger patients may have inappropriately overactive cardiac and autonomic responses.

Clinical importance. There appear to be distinct pathophysiologies underlying vasovagal syncope in different age groups. The pathophysiology in young people appears to be characterized by excessive cardiac and autonomic responses to stress, whereas in older patients, the pathophysiology appears to be a more generalized cardiovascular decline, with attenuated cardiac and autonomic responses to stress.

Therapeutic pacing can compensate for and correct bradycardia. Preliminary data suggest that pacing may have a

Table 2. Comparison of Final Outcomes in the 36–64 and ≥65 Years-Old Groups With Respect to the ≤35 Years-Old Group

Tilt-Test Response	36–64 Years (n = 169) OR (CI)*	≥65 Years (n = 171) OR (CI)*	p Value
Incomplete tilt test	8.8 (2.36–32.8)	7.63 (2.10–27.8)	0.0024
Negative tilt test	NS	NS	NS
Mixed response (VASIS-1)	NS	NS	NS
Cardioinhibitory response (VASIS-2A)	NS	NS	NS
Severe cardioinhibitory response/asystole (VASIS-2B)	0.34 (0.19–0.60)	0.18 (0.076–0.41)	< 0.0001
Pure vasodepression (VASIS-3)	4.4 (0.508–38.8)	29.5 (3.9–22.4)	< 0.0001

*Odds ratio (OR) with 95% confidence interval (CI) compared with the ≤35 years-old group (n = 165).
NS = no significant association; other abbreviation as in Table 1.

beneficial role in preventing and/or delaying syncope in those with significant bradycardia (cardioinhibition) revealed by tilt testing (13–16). Negatively chronotropic agents, especially beta-blockers, may be beneficial for controlling excessive tachycardia. Fluid-retaining drugs, such as fludrocortisone, and vasoconstrictive drugs, such as midodrine, may be useful in those in whom hypotension is the primary problem. These patients may also benefit from support stockings.

Non-invasive or non-pharmacologic approaches may also have a role. Tilt training appears to help in selected patients (17). It may be possible to use voluntary cortical mechanisms to dampen and/or compensate for cardiac/autonomic reflex effects.

These results need now to be seen in the light of the recently published International Study on Syncope of Uncertain Etiology (ISSUE) (18). In relatively small numbers of patients, the use of an implantable loop recorder has shown that asystole is more frequently associated with spontaneous syncope than with tilt-induced syncope. The data from ISSUE need amplification. However, the data presented here remain valid in a physiological sense and pertinent for the selection of therapy. When more data from implantable loop recorders are available, it is likely that the observations presented will apply.

Study limitations. It may be considered important to ensure that the findings of the test are reproducible. We did not repeat the test in our patients. It is unclear whether individual tilt-test responses are reproducible (19). Repeat tilt testing for diagnostic purposes may have a limited role. Once patients have been tilted, their responses may change because they are aware of what to expect and attempt to respond. There is also an absence of a control group (i.e., age-matched subjects without syncope of unknown origin).

There are other changes in the vasovagal response, such as respiratory patterns (20). These may also vary according to age. However, at present, the two changes that can be most accurately and readily measured are HR and BP; hence, the study has been confined to these.

Reprint requests and correspondence: Dr. Arvinder S. Kurbaan, Department of Cardiology, London Chest Hospital, Bonner Road, London E2 9JX, United Kingdom. E-mail: a_kurbaan@hotmail.com.

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